Are friends really the family we choose? Local variations of hypothalamus activity when viewing personally known faces

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Are friends really the family we choose? Local variations of hypothalamus activity when viewing personally known faces

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ABSTRACT

Sibling and friend relationships have significant impact on individuals' socio-emotional development. Hypothalamic supraoptic nucleus (SON) and paraventricular nucleus (PVN) synthesize and secrete neuropeptides, including oxytocin, associated with attachment behaviors. Here, using fMRI, we investigate the implication of these two hypothalamic nuclei in the visual processing of personally known faces. Faces of same-sex sibling, best friend, celebrity, and unknown person appear in the middle of the screen while participants perform a task requiring a button click each time a central white dot turns red. Ratings of familiarity (time spent together) and emotionality (feelings toward individual) toward the four individuals are recorded. Local activation within the hypothalamus is assessed via two complementary methods: (1) voxel-based analyses within inclusive mask of the hypothalamus; (2) region-of-interest (ROI) analysis of partial hypothalamic volumes using SON and PVN as center of mass coordinates, with percent signal change extracted and analyzed within these ROIs. Results suggest that the SON responds to all familiar individuals while the PVN has increased response to sibling compared to friend faces and is correlated to familiarity but not emotionality. These findings support differential involvement of local hypothalamic substructures SON and PVN in response to faces of individuals with different social relationships.

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"Friends are the family we choose for ourselves." *Edna Buchanan*

Codependency with other humans is an essential part of human life. More interestingly, humans tend to categorize and place different significance to individuals that make up their social circle (Laursen & Bukowski, 1997). Humans rely on interactions with others not only for survival but also for development and general well-being. Human infants are born unable to care for themselves and therefore rely on the efforts of caregivers, typically family members, for survival. Over time and experience, humans expand their social circle beyond kinship by bridging close, meaningful relationships with other human beings known as friendship. The distinction between a family member and a friend is the biological affiliation, but subjective experience with each individual may lead to different attachment and emotional significance. Much is known about the importance of parental relationships for optimal psychosocial development (Bornstein, 2002). Relationships with siblings and friends, which can be compensatory or complementary, have also been shown to have significant impact on socio-emotional development that shapes future interpersonal relations (Sherman, Lansford, & Volling, 2006).

Attachment appears to be a major factor to form and sustain such enduring relationships. Oxytocin (OXT) has been shown to have a pivotal role in promoting attachment and affiliative behaviors (Heinrichs & Domes, 2008). This neuropeptide is synthesized and secreted by the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus. OXT acts peripherally in the bloodstream and centrally through axonal connections to other brain areas including the amygdala, striatum, nucleus accumbens, and hippocampus, involved in social motivation and reward processing (Skuse & Gallagher, 2009). Moreover, hypothalamic abnormalities, specifically in the PVN, have been linked to autism spectrum disorder (Wolfe, Auzias, Deruelle, & Chaminade, 2015), a disorder with marked social impairments.

Social and emotional attachments influence face processing. Brain areas associated with attribution of personal traits and mental states to others as well as autobiographical memory retrieval were activated when viewing personally familiar (family and long-

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term friends) faces, as compared to celebrity faces (Gobbini, Leibenluft, Santiago, & Haxby, 2004). Areas in the visual, frontal, and medial parietal cortices were involved in the discrimination of kin from non-kin faces (Platek & Kemp, 2009), which was interpreted as an evolutionary adaptation to avoid incest. A positron emission tomography study found activation of the hypothalamus during personally familiar face-detection task, which they postulated to be related to increased emotional response (Sugiura, Kawashima, Nakamura, Sato, & Nakamura et al., 2001). Altogether, these findings demonstrate that the processing of faces differs depending on the personal significance of each face to the individual, with a clear distinction between personally and impersonally known faces, and also between highly attached kin and non-kin faces. Furthermore, an fMRI study showed correlation between peripheral OXT and hypothalamic activity when mothers viewed own infant faces versus unknown infants (Strathearn, Fonagy, Amico, & Montague, 2009), demonstrating a link between hypothalamic activity and secretion of OXT when viewing highly attached faces. However, no study to date specified the precise substructure within the hypothalamus, perhaps because of the challenges associated with measuring the activity of small brain structures with fMRI.

Here, we devised methods in fMRI to investigate local activity within the hypothalamus focusing on the two OXT-synthesizing nuclei, SON and PVN, in response to implicit processing of four categories of faces: Sibling (Sib), Best friend (Fri), Celebrity (Cel), and Unknown (Unk), all gender-matched to our adult participants. Celebrity serves as a visually familiar face but with no history of personal interaction with the participants in order to control for familiarity bias for sibling and close friend compared to unknown person. Participants are instructed to fixate a white dot and to click as quickly as possible when it turns red while stimuli are presented in the center of the screen. Familiarity and emotionality of the four categories of individuals are assessed based on a revised version of the familiarity and emotionality (FAE) questionnaire (Platek & Kemp, 2009). Familiarity in the questionnaire is defined as time spent with the individual at present (not the long-term history), while emotionality measures their feelings toward the individual.

To measure the activity of these hypothalamic substructures, we use two complementary methods: (1) voxel-based analysis within masks of the gray matter and of the hypothalamus and (2) region-of-interest (ROI) analysis, through the extraction of percent signal change (PSC) in hypothalamic volumes centered on the coordinates of SON and PVN center of mass (Baroncini, Jissendi, Balland, Besson, & Pruvo et al., 2012). We hypothesize that increased SON and PVN activity should be observed in sibling and friend faces as compared to celebrity and unknown faces. We further postulate that variations in the activity of SON and PVN between sibling and friend would correlate with their familiarity and emotionality scores.

Methods

Subject

A total of 23 adults were recorded but three were excluded from the analysis due to excessive movement (>2 mm according to ARTifact detection tool (www.nitrc.org/projects/artifact_detect)) during fMRI scanning. The final sample included 20 right-handed participants including six males, mean age of 25.2 years old (range = 19–30, SD = 3.14). Participants had no prior history of severe illness or psychiatric disorder, and none of them was on medication at the time of experiment according to self-report. All had a secure attachment style except for one who was coded as ambivalent, according to the French version of Adult Attachment Scale (Bouthillier, Tremblay, Hamelin, Julien, & Scherzer, 1996). They were recruited online through web and email advertisements at the Aix-Marseille University and compensated 50 euros. Each participant gave a written informed consent. This study was approved by the local ethics committee (Comité de Protection des Personnes Sud Méditerranée I, approval number 130004).

Stimuli

Faces of individuals with varying familiarity and emotional significance to the participants were categorized into four conditions: Best Friend (Fri), Sibling (Sib), Celebrity (Cel), and Unknown (Unk). Participants identified one individual that they consider their best same-sex friend and one same-sex sibling (if they had more than one). To ensure similar shared sibling experiences across participants and to reduce the effects of generational gap, they were asked to choose a sibling with no more than 10 years age difference. They then provided nine different naturalistic, colored pictures of the same individual from each of these categories with the instructions that the pictures should be recent (<5 years), display positive emotion (smile with or without teeth), and facing forward to show full facial features (eyes, nose, and mouth), without photographic edits and distractive elements (such as sunglasses or face paints). For the unknown category, nine pictures of one unknown male

or female individual within the same age group were selected and gender-matched with participants. For the celebrity category, the selection process involved providing pictures of several sportsmen and their partners to 20 individuals (some of them were later included as participants) for identification. David and Victoria Beckham were rated to be the most familiar based on participants' overall correct response. We then verified the familiarity of the chosen celebrities with our participants by asking them to identify the person in the photo provided before the experimental session. The participants were all able to name the celebrity. Participants verbally reported no extreme sentiment (positive or negative) toward the celebrity. Celebrity was gender-matched with participants.

Selected pictures were cropped to show only the face and neck. Each face was scaled to fit in a 14 cm height by 11 cm width oval template using Photoshop software (San Jose, CA). Cropped faces resulted in a field of view (FOV) of 13° by 10° when projected in the scanner. Images were standardized for luminosity with the mean pixel value set at 100 (Photoshop unit) by averaging the RGB colors in all pixels in order to obtain a constant global luminosity. Some of the pictures required further edit to remove glare and red-eye effect. On a black background, white or red dot (0.25 cm, FOV 2°) required for the behavioral task was placed in the center of the screen. Each picture was then positioned so that the dot was located exactly between the eyes to maximize eye contact.

Experimental paradigm

Participants were scanned at Marseille Functional MRI center. Each session consisted of briefing, training, questionnaire completion, and approximately an hour of scanning for a total of 1.5 h.

They were presented with stimuli while performing a behavioral task. Each run was made up of three blocks of each of the conditions Fri, Sib, Cel, and Unk (three stimuli per block, presented 5 s each), resulting in a total of 12 blocks with all 36 possible stimuli from all four conditions. A variable inter-block interval (3.73 s–5.73 s, m = 4.73 s), which consisted of a fixation frame (blank screen with white dot) followed by a countdown cue (yellow dots in 3, 2, 1 order of 533 ms each, 1.6 s total) was included. There were six runs altogether, which summed up to approximately 30 min of total functional scanning time. Trial randomization across participants was preprogrammed so that all of the stimuli appeared an equal amount of time.

Participants had to fixate the white dot and click on the button with their right thumb as quickly as possible when the dot turned red. The red dot appeared four times within each block for 333 ms each (at least 2 s apart), starting at least 333 ms after the first stimuli onset and no later than 333 ms before last stimuli offset. The face stimuli were processed implicitly while this task served to ensure fixation consistency throughout the experiment. Participants were given a short version of the task using celebrity stimuli before entering the MRI scanner.

Participants filled a revised version of familiarity and emotionality questionnaire (Platek & Kemp, 2009) before and after the scanning. The questionnaire was translated into French and adapted to include celebrity and unknown in addition to sibling and best friend. The questionnaire was divided into two sections: one question for familiarity and 21 likert-style questions to measure emotionality. For familiarity, they reported the time spent with the individual at present. For emotionality, they reported their general feelings toward the individual to questions such as "I like spending time with this person" and "I would do anything for this person."

fMRI acquisition

Imaging data were acquired from a 3T BRUKER MEDSPEC 30/80 MRI scanner at Marseille Functional MRI center. After MRI compatibility screening and removal of metallic objects, participants were moved to the scanning room and given earplugs to dampen the noise during scanning. The experiment was played from a computer in the control room to a translucent screen at the back of the scanner through a projector. While lying supine on the scanning bed, participants viewed the projected stimuli from an angled mirror attached to the head coil, which was adjusted to individual viewing comfort. They were instructed to remain still throughout the scanning. Responses were recorded with an MRI-compatible thumb response button.

Eight MRI acquisitions were performed. First, a fieldmap using a double echo FLASH sequence recorded distortions in the magnetic field (FLASH, FOV 192 × 192 × 192 mm^3, voxel size 3 × 3 × 3 mm^3, TR 30.0 ms, TE 3.700 ms, $\alpha = 30°$). Six functional runs each comprising 122 volumes (Echo-Planar Imaging [EPI], AQ2 FOV 192 × 192 mm^2, pixel size 3 × 3 mm^2, 36 interleaved ascending axial slices and each were 3 mm thick without gap, TR 2400.0 ms, TE 30.000 ms, $\alpha = 81.6$) with the same spatial parameters as the fieldmap, encompassing the whole brain parallel to the AC-PC plane, were recorded. Finally, we acquired high-resolution T1-weighted anatomical images of each participant (MP-

RAGE, FOV 256 × 256 × 180 mm^3, voxel size 1 × 1 × 1 mm^3, TR 9.4 ms, TE 4.424 ms, α = 30°).

MRI data processing

fMRI data were analyzed using SPM12 and toolboxes (www.fil.ion.ucl.ac.uk/spm). Slice time correction was done to correct for the different timing in image acquisition within the same functional volume. Fieldmap toolbox (Hutton et al., 2002) was then used to correct for EPI image distortions caused by movements and magnetic field inhomogeneity. We removed the first four EPI images to allow for initial T1 equilibrium. Images were then realigned and unwarped, taking into account voxel displacement map obtained from the Fieldmap. These images were used for the single-subject level of analysis. Each block was modeled as a 15 s boxcar function synchronized with the onset of the first condition image, and the button clicks as event-related. The condition regressors were convolved with the canonical hemodynamic response function. In order to remove low-frequency drifts in the BOLD signal, a high-pass filter with a cutoff period of 128 s was applied to the voxel time courses.

Anatomical images were segmented (VBM8) for diffeomorphic inter-subject registration using DARTEL toolbox (Ashburner, 2007), providing individual deformation fields to transform individual beta images in a common DARTEL space for the second-level analysis. A 5 mm Gaussian kernel spatial smoothing and thresholding at 0.75 of the last DARTEL template (gray matter probability in DARTEL space) was used to make a mask of gray matter in DARTEL space (GM). Segmented MNI_Colin27 image was added to the DARTEL space to obtain deformation fields between the DARTEL space of the analysis and the Montreal Neurological Institute (MNI) space. A hypothalamus mask manually delineated by four independent observers on MNI_Colin27 template (Wolfe et al., 2015) was transformed into DARTEL space using this deformation field.

For second-level voxel-based analysis, individual beta images corresponding to the four conditions were deformed into our DARTEL space with isomorphic 1 mm^3 voxels with a large smoothing kernel (8 mm^3) for the whole brain analysis using the gray matter mask (GM) and a small smoothing kernel (2 mm^3) for the analysis within the hypothalamus mask. A repeated measure analysis of variance (rmANOVA) was performed for both analyses including conditions as factor of interest and sessions as random factors. We tested the effects of the following contrasts: (1) familiar versus unfamiliar faces (Sib–Unk, Fri–Unk, Cel–Unk); (2) personally familiar versus famous familiar (Sib–Cel, Fri–Cel), and (3) between personally familiar (Sib–Fri) and (Fri–Sib). Results were thresholded at $p < 0.05$ family-wise error (FWE) corrected at the peak level, with a minimal extent threshold of 30 voxels for GM mask and 10 voxels for hypothalamus mask. Significant clusters were transformed into MNI space using DARTEL deformation to obtain MNI coordinates reported in the tables. For the hypothalamus nuclei attribution, we used the Euclidean distance between the clusters' MNI peak coordinate and previously published center of mass coordinates for hypothalamus nuclei (Baroncini et al., 2012).

For validation, we used an ROI approach. Due to the small size of our nuclei of interest and limited image resolution, thus posing delineation challenges, we divided the hypothalamus into volumes that include our nuclei of interest. We thus defined three ROIs: an anterior-ventral hypothalamus box (avHyp) that includes the SON, an anterior-dorsal hypothalamus box (adHyp) that includes the PVN, and a posterior-ventral hypothalamus box (pvHyp) that includes the mammillary body (MMB).

To maximize standardization while ensuring that these nuclei of interest are entirely included in our ROIs, boxes were created larger than their anatomical sizes (review Schindler, Geyer, Strauß, Anwander, & Hegerl et al., 2012) and standardized for total volume. We first created boxes in MNI space based on *a priori* center of mass coordinates of nuclei of interest (*x*, *y*, *z* = 6. -0.5. -15; 2. -2. -11.5; and 3.5. -6. -16. for the avHyp; adHyp; and pvHyp, respectively) from Baroncini et al. (2012) using MarsBAR. We then referred to the histological atlas with scale bars (Baroncini et al., 2012) and hypothalamic parcellation from MRI dataset (Makris et al., 2013) for the extent, shape, and orientation of ROIs. The boxes for each side (left and right) of the nucleus (in *x*, *y*, *z*) were: 5 mm × 6 mm × 3 mm flat boxes for avHyp and 3 mm × 5 mm × 6 mm elongated boxes for adHyp and 6 mm × 5 mm × 3 mm flat boxes for pvHyp, in accordance to the anatomical shapes and orientation of the respective nuclei. The volume of each box was 90 mm^3.

These MNI ROIs were transformed into DARTEL space. In DARTEL space, new ROI boxes, with similar geometric constraints as the MNI ones, were created, taking into account the center of gravity after spatial transformation in DARTEL space. As DARTEL transformation resulted in a reduction of the ROIs volume around 75 mm^3 (DARTEL space shrunk as compared to the MNI space), the largest dimension of each ROI was reduced from 6 mm to 5 mm. Each ROI included 75 1 mm^3 voxels. The ROIs were rendered on DARTEL space anatomy to confirm localization visually. The avHyp was above the optic tract, the adHyp was along the third ventricle while the pvHyp included the

clearly identifiable mammillary body bumps, consistent with their anatomical locations. The ROIs were used to confirm the attribution of clusters to hypothalamic nuclei, by calculating the percentage of activated clusters actually located within the ROI. These ROIs were also used for event-related PSC extraction with MarsBAR. rmANOVA using conditions and lateralization as factors of interest and sessions as random factor were computed in SPSS to verify the effect of conditions. To investigate the effect of behavioral variable on the ROI response, another rmANOVA was ran using the difference in PSC between friend and sibling as variable, the difference in emotionality and familiarity scores between friend and sibling as covariate, and the lateralization as factor of interest with sessions as random factor. Reaction time was analyzed using SPSS with rmANOVA, with conditions and sessions as factors.

Results

Behavioral

Reaction time analysis revealed a main effect of condition $F(3, 15) = 8.34$, $p = .002$ but not session $F(5, 13) = 1.31$, $p = .319$ on reaction time, showing that even implicitly processed, stimuli category affected behavior. Reaction time recorded during performance of the task was the slowest for unknown faces (mean = 411 ms, standard deviation = 79) and showed gradual time decrease with familiarity; celebrity (404 ± 78 ms), friend (399 ± 73 ms), and sibling (393 ± 76 ms). A *post-hoc* Bonferonni test revealed that there was significant difference in reaction time to faces of Fri versus Unk ($p = .017$) and Sib versus Unk ($p \leq .001$) but not for Cel versus Unk ($p = .640$). No significance was found in other pairwise contrasts.

GM analysis

Whole brain analysis using an inclusive gray matter (GM) mask was used to verify the processing of faces. Main effects revealed activation in the fusiform gyrus, consistent with previous literature of face processing (Kanwisher & Yovel, 2006). With the exception of Sib–Fri and Fri–Sib, we found significant brain activations for different contrasts, which support that our experimental conditions were processed differently (Figure 1, Table 1).

Hypothalamus mask analysis

Voxel-based analysis within the hypothalamic mask revealed significant clusters of activation for different

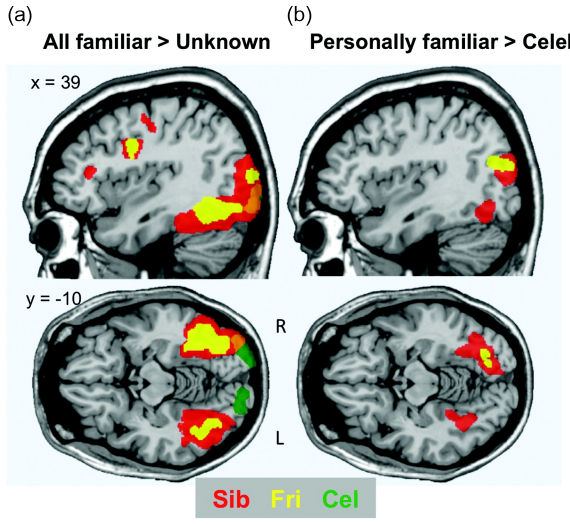

Figure 1. Activation maps for the contrasts (a) each familiar faces versus unknown showing more overlapping areas between sibling and friend in the fusiform gyrus, inferior occipital gyrus bilaterally, and the right intra-parietal sulcus; (b) each personally known faces versus celebrity still showing overlapping areas in the right fusiform gyrus, inferior occipital gyrus, and intra-parietal sulcus. Orange area reflects the overlap between Sib versus Unk and Cel versus Unk. Maps are rendered on Colin template.

contrasts, suggesting differential local activity within the hypothalamus in response to the faces in our conditions. Distance between the clusters' peak and the center of hypothalamus nuclei (Table 1; Baroncini et al., 2012) was used to attribute clusters to hypothalamic nuclei. For contrast Sib versus Unk, significant activation was found in a cluster attributed to the right SON, while no cluster was attributed to the right SON for Fri versus Unk. Significant activation was found in the left SON for Fri versus Unk. Contrast Cel versus Unk showed bilateral activation of the SON. For contrast Sib versus Fri, significant activation was attributed to right PVN (Table 2). A cluster attributed to the right PVN was found in the contrast Sib versus Cel, MNI (x, y, z) = 5, 1, −11, but did not reach significance ($P_{FWE} = .200$). No significant activation was found in the contrast Fri versus Cel.

Attributions to hypothalamus nuclei were verified using the ROI boxes, which were created based on the center of mass coordinates of each nucleus to ensure that thresholded activation clusters are within these boxes. Congruent with the cluster attributions based on the peak coordinates, our activated clusters fell at least partially within the corresponding ROI, thus confirming that the attributions of respective nuclei are reliable. Illustration and percentage of our activated

Table 1. Significant BOLD activations in the global brain for the various contrasts ($P_{FWE} < 0.05$, cluster size >30).

Contrast	L/R	Brain area	*T*	Volume (mm^3)	Coordinates *x y z*		
Sibling > Unknown							
	R	Intraparietal sulcus	8.32	33,117	33	−68	28
	R	Inferior occipital gyrus*	7.85	22,374	40	−64	−16
	R	Fusiform gyrus*	7.02	319	33	-53	-20
	R	Precuneus*	6.14	1390	27	−57	50
	L	intraparietal sulcus	7.91	1820	−30	−81	21
	L	Inferior occipital gyrus*	7.36	737	−35	−74	−13
	L	Fusiform gyrus*	6.14		−36	−57	−13
	L	Pulvinar	6.06		−18	−34	1
	R	Inferior frontal gyrus	5.69		50	27	13
	R	Precentral gyrus	5.63		38	−2	31
	R	Middle frontal gyrus	5.45		30	4	5
Friend > Unknown							
	R	Fusiform gyrus	6.42	4580	36	−53	−15
	R	Intra-parietal sulcus	5.72	1722	34	−72	34
	R	Inferior occipital gyrus*	5.00	1412	33	-86	17
	L	Inferior occipital gyrus	5.09	777	−33	−84	−17
	L	Fusiform gyrus*	5.04		−36	−53	−21
	R	Middle frontal gyrus	5.03		45	9	35
	R	Precuneus	4.88	182	27	−58	49
Celeb > Unknown							
	R	Inferior occipital gyrus	8.24	5216	25	−95	−4
	L	Lingual gyrus	6.58	3481	−12	−86	−4
Sibling > Celeb							
	R	Intraparietal sulcus	7.60	16,905	33	−71	23
	R	Lingual gyrus*	6.68	8962	24	−76	−4
	R	Fusiform gyrus*	5.43	1341	35	−61	−16
	L	Inferior occipital gyrus	7.08		−30	−82	17
	L	Fusiform gyrus	5.41		−34	−54	−13
Friend > Celeb							
	L	Inferior occipital gyrus	6.35	1636	−36	−82	18
	R	Intra-parietal sulcus	5.75	1619	33	−71	23
	R	Fusiform gyrus*	5.08	265	35	−60	−20
	R	Cuneus	5.24	504	12	−87	11
	R	Lingual gyrus	5.08		21	−73	−7

*Indicates subcluster of the above.

Table 2. Significant BOLD activations in ROIs within the hypothalamus mask ($P_{FWE} < 0.05$, cluster size >10).

Contrast	L/R	Hypothalamic nucleus	*T*	Volume (mm^3)	Coordinates *x y z*	Distance from nucleus	% in ROI
Friend > Unknown	L	SON	4.05	15	−6, 3, −16	2.2	93
Sibling > Unknown	R	SON	6.14	74	8, 3, −16	2.7	46
Celebrity > Unknown	R	SON	4.09	33	8, 5, −14	5.4	36
	L	SON	3.88	13	−6, −1, −16	1.4	100
Sibling > Friend	R	PVN	4.20	30	3, 1, −10	3.5	70
	R	SON*	3.63	14	5, 1, −16	1.6	100

SON: supraoptic nucleus, PVN: paraventricular nucleus.
*Indicates a cluster that did not reach significance threshold ($p = .064$).

clusters in each region for the contrasts can be found in Figure 2 and Table 2, respectively.

ROI analysis

To validate the response of hypothalamus nuclei to the experimental conditions, rmANOVA was computed to measure the effects of condition and laterality on the PSC extracted from the ROIs. For avHyp, results revealed significant main effect of laterality $F(1,19) = 7.47$, $p = .013$, close to significance effect of condition $F(3,17) = 3.00$, $p = .06$, and a significant interaction between laterality and condition $F(3,17) = 3.81$, $p = .03$. For adHyp, no significant main effect was found for laterality $F(1, 19) = 0.47$, $p = .50$ and condition $F(3, 17) = 0.19$, $p = .90$, while there was a significant interaction between laterality and condition $F(3, 17) = 3.29$, $p = .046$. For pvHyp, no significant effect of laterality $F(1, 10) = 0.46$, $p = .50$, condition $F(3, 17) = 1.73$, $p = .20$ or interaction $F(3, 17) = 0.44$, $p = .73$ were found (Figure 3(c)).

Pairwise comparisons results showed significant difference in the left avHyp between Fri and Unk ($p = .002$) and Fri and Cel ($p = .027$) and no difference

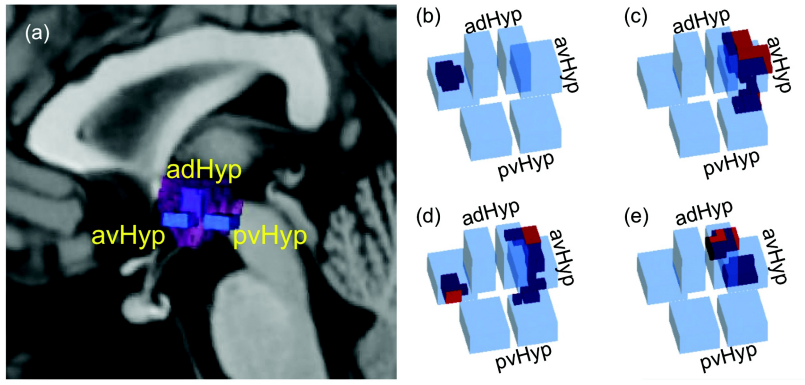

Figure 2. (a) Location of the left hemisphere regions of interest and hypothalamus mask rendered on Colin template. Activated clusters overlapped with ROIs for the contrasts (b) Fri versus Unk, (c) Sib versus Unk, (d) Cel versus Unk, and (e) Sib versus Fri; (b–e) are seen from a posterior/dorsal/left point of view and in neurological convention (left avHyp is on the left side). avHyp: Anterior-ventral hypothalamus (contains SON), adHyp: anterior-dorsal hypothalamus (contains PVN), pvHyp: posterior-ventral hypothalamus (contains MMB).

between Fri and Sib (p = .197). No significant difference was found between Sib and the two control conditions. This means that the left avHyp responds more to friend faces when compared to control conditions but not to sibling faces. On the other hand, significant difference between Sib and Unk (p = .030) in the right avHyp was found but not between Sib and Cel (p = .409) and Sib and Fri (p = .546), in agreement with the absence of significant result for this contrast in Table 2. No significant difference was found between Fri and control conditions. This means that significant increase of PSC was observed only for sibling faces, but not for the other two familiar faces, when compared to unknown (Figure 3(a)). No significant effects of pairwise comparisons between experimental conditions were found for left and right adHyp (Figure 3(b)).

Furthermore, we assessed whether reaction times to the categories of stimuli could be related to the response in our hypothalamic regions of interest by calculating Pearson's correlation between reaction times for each condition, session, and participant with the bilateral activity in our three regions of interest. None of these correlations were significant (all ps > .3).

FAE questionnaire

Analysis of the FAE scores showed a main effect of familiarity $F(3,79)$ = 179.1, p < .001 and emotionality scores $F(3,79)$ = 122.5, p < .001 between conditions. Post-hoc Bonferonni-corrected pairwise comparisons revealed no significant difference between Sib and Fri (p = .230) for familiarity scores, while difference was found for all other pairwise conditions (p < .001), showing reduced familiarity for Cel and Unk faces, respectively (Figure 4(a)). For emotionality scores, significant differences were found in all pairwise comparisons of conditions (p < .010), reporting highest emotionality for Fri compared to Sib, Cel, and Unk (Figure 4(b)).

PSC and FAE correlation of personally known faces

To further understand the response of SON and PVN to the two conditions of interest, that is, Sib and Fri, we investigated the relationship between PSC in the adHyp and avHyp and FAE scores. The distribution of the familiarity scores reflects that the differences between the two conditions vary in direction (Sib > Fri or vice versa; Figure 4(c,d)). As no group difference was found in the familiarity score and in the contrast between Sib and Fri in the adHyp (ROI including the PVN), we hypothesized that activity in these two conditions is related to individual familiarity or emotionality scores rather than their category. We therefore tested whether the *difference* in the mean PSC of the adHyp and avHyp between Sib and Fri for each subject correlates with the *difference* in their respective FAE scores for the two conditions. We conducted a rmANCOVA to analyze PSC difference between Sib and Fri with laterality as factor of interest and session as random factor, using differences in familiarity and emotionality scores as covariates. For avHyp, results revealed no effect of familiarity ($F(1,18)$ = 0.59, p = .454), or emotionality ($F(1,18)$ = 0.10, p = .752) nor interaction with laterality of the ROI ($F(1,18)$ = 0.56, p = .464 and $F(1,18)$ = 3.72, p = .070, respectively). For adHyp, a significant effect of familiarity was found ($F(1,18)$ = 8.62, p = .009) with no significant interaction between laterality and familiarity ($F(1,18)$ = 1.04, p = .322), but no main effect or

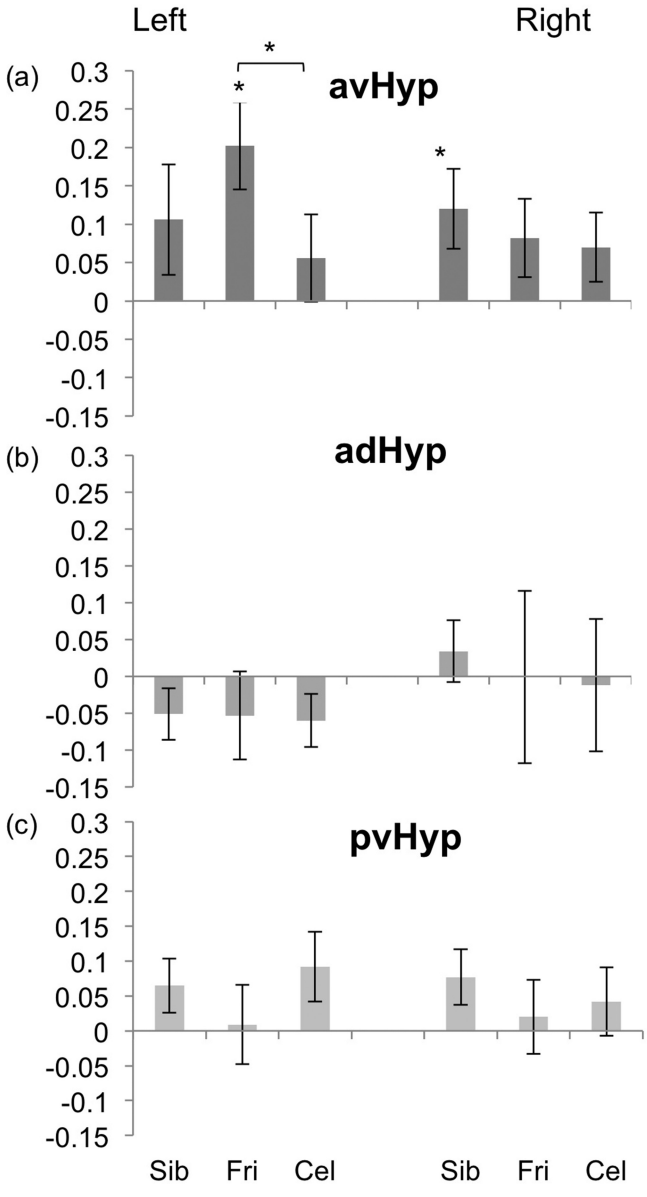

Figure 3. Mean (± SEM) percent signal change (PSC) across familiar conditions subtracted from baseline (unknown faces) in ROIs (a) left and right avHyp, (b) left and right adHyp, and (c) left and right pvHyp. * indicates significant difference ($p < .05$). avHyp: Anterior-ventral hypothalamus (contains SON), adHyp: anterior-dorsal hypothalamus (contains PVN), pvHyp: posterior-ventral hypothalamus (contains MMB).

interaction in the case of emotionality ($F(1,18) = 0.39$, $p = .542$ and $F(1,18) = 0.18$, $p = .674$). Regression analysis of mean PSC in bilateral adHyp against familiarity yielded a R^2 of .32 (Figure 5).

Discussion

Main effect of familiarity and validation of the experimental paradigm

Results of the whole brain analysis showed an increased response to personally familiar faces in the fusiform gyrus, an area involved in face processing (Kanwisher & Yovel, 2006). Moreover, significant overlapping areas of activations between sibling and friend were found in the fusiform gyrus and the inferior occipital gyrus, when compared to celebrity and unknown. These areas are associated with early identification of faces and recognition of identity (Haxby, Hoffman, & Gobbini, 2000). Activation was also found in the intraparietal sulcus and middle frontal gyrus, areas involved in attention orientation (Chica, Bartolomeo, & Lupiáñez, 2013). We suggest that early recognition of personally known faces may trigger automatic orientation to these faces, thus requiring additional attentional resources to fixate the dot during the task. This enhanced voluntary attention may explain increased task performance reflected by faster reaction times for sibling and friend faces.

Summary of results for the hypothalamus

The present fMRI study investigated the involvement of the hypothalamus focusing on the SON and PVN, both containing neurons that synthesize and secrete OXT, in processing sibling and friend faces with unknown faces as controls. To dissociate between personally known faces and other familiar faces, we included celebrity faces that were visually familiar but with no personal affiliation. We hypothesized that significant increase of SON and PVN activity should be observed in Sib and Fri compared to other conditions with minimal attachment and social significance, and that the difference between them will be related to the degree of familiarity and emotionality. The results of this study revealed significant activity of hypothalamic regions of interest containing nuclei SON and PVN in response to various faces.

First-level analysis was performed in individual participant's acquisition space. A diffeomorphic approach (DARTEL) was used to optimize spatial precision of our inter-subject registration of beta estimates generated in participants' space. Minimal smoothing of 2 mm was applied to improve the local signal to noise ratio without compromising spatial resolution. Results from our voxel-based analysis within the hypothalamus mask demonstrated localized activation clusters at very stringent thresholds. Nuclei attribution was based on the distance between the clusters' peak coordinates and the nuclei center of mass coordinates (Baroncini et al., 2012). To provide more

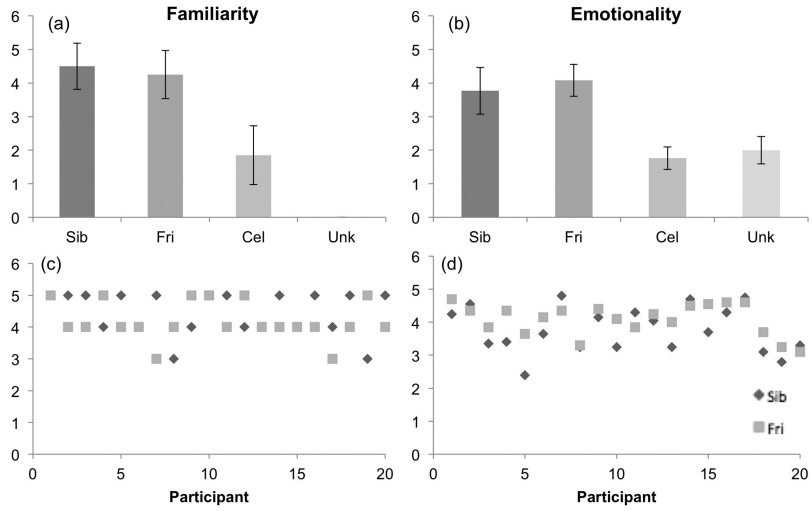

Figure 4. Mean (± SEM) familiarity (a) and emotionality (b) scores in the four experimental conditions. Lower panel depicts the distribution of (c) familiarity and (d) emotionality scores for sibling and friend for each subject, showing varying relationships for the two conditions across subjects. Single points in (c) are overlapping scores between sibling and friend.

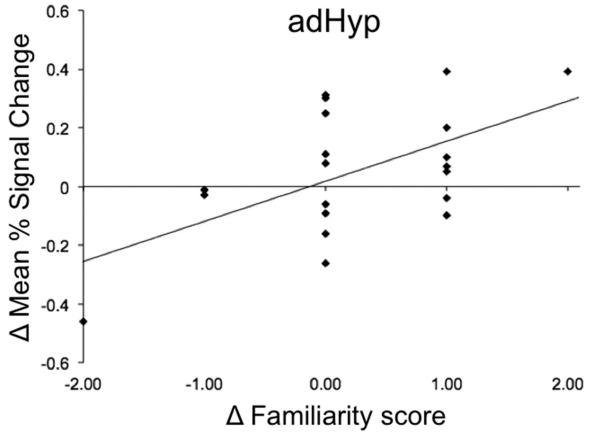

Figure 5. Correlation of the difference in bilateral percent signal change between sibling and friend with difference in familiarity scores in the adHyp (anterior-dorsal hypothalamus, contains PVN).

reliable evidence to support our voxel-based results showing activations in regions corresponding to the SON and the PVN, we created ROI boxes including these nuclei (avHyp and adHyp, respectively) and another ROI box containing the mammillary body (pvHyp) as control. Further analysis showed corroborating results reflected by the percentage of activated clusters found within the boxes (Figure 2). Additionally, the PSC analysis results (Figure 3) showed significant effects related to experimental conditions only in avHyp (includes SON) and adHyp (includes PVN) but not in the pvHyp (includes MMB), also in agreement with previous analyses. Altogether, the findings from these two independent approaches provide converging evidence that validates differential activity in ROIs including SON and PVN in response to the different categories of faces.

Local response of hypothalamic nuclei SON and PVN

In the hypothalamus mask analysis, increased activation attributed to SON was observed for all familiar faces when compared to unknown faces, which suggests that the SON responds to all familiar faces regardless of the level of attachment or person knowledge. However, activations were shown specifically in the left side for friend, right for sibling, and bilaterally for celebrity (Table 2). The bilateral response to celebrity faces was surprising considering that celebrity had the least social significance compared to sibling and friend. Also, lateralization of SON activity in response to sibling and friend in the right and left, respectively, was unexpected, and could imply hemispheric differentiation of hypothalamus response for these two personally known faces. The results of percent signal analysis confirmed this lateralization, showing specific response in the right avHyp for sibling and left avHyp for friend (Figure 3), referring to the anterior and ventral region of interest comprising the SON. While no prior hypotheses were made for lateralization of hypothalamic response, lateralization has been reported when processing socio-emotional stimuli (Adolphs, 2002). Hypothalamus activity has also been reported in the left hemisphere when viewing own infant child face (Strathearn et al., 2009) congruent with our finding for friend faces, both sharing similarities in terms of high emotionality but

relatively limited time known (friend compared to sibling, own newborn compared to other newborn faces), and in the right when viewing all personally known faces (Sugiura et al., 2001).

For the activations attributed to the PVN, voxel-based results indicated that only sibling faces compared to friend faces evoked stronger response in the right hemisphere (Table 2). The absence of significant PVN activity in any other contrast suggests that modulation of this nucleus' response only happens for personally familiar faces, while no conclusion can be reached about factors affecting its response to non-familiar faces with the current results. Our participants were mainly university students with closely aged best friend with an average of 7.9 years known and 22.9 years known for sibling. Therefore, it is certain that they have had more physical exposure and time to bond with their sibling than with their friend. Thus, despite the high amount of time spent with sibling and friend presently, it is plausible that longer exposure to sibling provides long-term effects that are absent for friends, regardless of present emotional report. In other words, the difference in PVN activity between sibling and friend found here may be related to prolonged interaction with sibling from early childhood through adulthood, as compared to the friend they met later on. Alternatively, PVN response to sibling could be due to kinship. Indeed, increased activity was also found between sibling and celebrity in the right PVN, but it did not reach significance threshold (p = .005 uncorrected). Previous animal study showed that the PVN is related to kin (maternal) behaviors implicating the OXT, showing disruption of maternal behaviors when the PVN was lesioned (Insel & Harbaugh, 1989), but the generalizability of this finding to the human population remains unknown. Percent signal analysis in adHyp, the ROI containing PVN, showed a limited effect of experimental conditions, as the significant interaction between laterality and conditions yielded no significant pairwise comparisons between conditions. However, it was revealed that *the difference in activity* between sibling and friend is correlated with *the difference in familiarity* (but not emotionality) scores between sibling and friend (Figure 5). Familiarity reflects the amount of time spent together in present time, suggesting that PVN response is more related to frequency of social interactions than feelings toward the individual. It is worth noting that *emotionality* is measured with a questionnaire that does not encapsulate every aspect of the term, a possible explanation for the absence of the hypothesized effect of emotionality on the activity of hypothalamus nuclei. It has been shown that social interactions influence neuroplasticity throughout lifetime (Kolb & Gibb, 2011), meaning that our affiliative encounters may influence neurodevelopment, including in adulthood. However, more investigation is required to clarify these two interpretations of whether or not PVN response is related to kinship or the physical time spent with the individual, in order to better understand the role of PVN in social relationships and affiliative behaviors.

Implications for the role of OXT-secreting nuclei in affiliative behaviors

Both SON and PVN synthesize and secrete OXT, a neuropeptide classically known to be involved in maternal bonding. However, other forms of consociate attachments such as those with siblings and friends also involve OXT (Feldman, 2012). While we did not directly measure the involvement of OXT, a previous study showed significant correlation between peripheral OXT and hypothalamic activity in fMRI (Strathearn et al., 2009). Here, we found increased response of PVN specifically toward sibling and friend faces, which may provide support for its involvement as part of the oxytocinergic system that mediates consociate attachments. The SON, on the other hand, responds to all visually familiar faces, suggesting that it has a more general function, perhaps as means to facilitate social interactions prior to the development of social attachments.

Aside from OXT, the SON and PVN also secrete arginine vasopressin (AVP), which was shown to have many similar positive social effects but also negative effects such as stress and anxiety (Heinrichs & Domes, 2008). With similar cytoarchitecture, both OXT and AVP neurons have axonal projections to the amygdala, hippocampus, and striatum, which are regions associated with emotion regulation, social cognition, memory as well as reward and motivation (review Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011), thus likely to influence social interactions and affiliative behaviors. Despite sharing commonalities as the two main OXT-secreting nuclei in the hypothalamus, the understanding of the mechanisms underlying differential SON and PVN involvement in social cognition can benefit from the current approach.

Limitations

Despite our efforts to optimize the methods to measure hypothalamic nuclei with such intricate structural organization, low spatial resolution of the fMRI is still an issue. Previous works have attempted to provide different qualitative methods for the mapping of

hypothalamic substructures (Baroncini et al., 2012; Makris, Swaab, Kouwe, Abbs, & Boriel et al., 2013; Schindler et al., 2013; Schönknecht, Anwander, Petzold, Schindler, & Knösche et al., 2013). In this study, the boxes used in our region of interest approach, i.e., avHyp, adHyp, pvHyp, were created based on strategic parcellation of hypothalamic subregions to include our nuclei of interest, with equal volume to standardize subsequent statistical analyses. Since the size and shape of each nucleus vary (Baroncini et al., 2012), these standardized boxes were created large enough to include the largest nucleus, which was the mammillary body at approximately 63.5 ± 17.6 mm^3 (Sheedy, Lara, Garrick, & Harper, 1999). Each box had an equal volume of 75 mm^3 using the center of mass coordinates of each nucleus to ensure that each of the boxes included the respective nuclei entirely, and tailored to their anatomical shapes and orientation to maximize accuracy. Inevitably, due to the varied sizes of our nuclei, ROI boxes for the smaller nuclei may include partial volume of neighboring nuclei, thus limiting interpretation of specificity in nucleus attribution. Nonetheless, this approach is useful in providing complementary evidence to support our voxel-based findings. Recent method (Schindler et al., 2017) using high resolution 7T MRI demonstrated an improved evaluation of the hypothalamic boundaries, which will be relevant in future research. Another limitation of this study is the sample size, which precludes the investigation of gender differences (Mcrae, Ochsner, Mauss, Gabrieli, & Gross, 2008 for review) as well as hormonal cycle in women, which has been shown to impact the hypothalamic–pituitary–adrenal circuitry (Goldstein et al., 2005), in response to social stimuli.

Conclusion

Our study revealed similarities in the global brain processing of friend and sibling faces reflected by results of the whole brain analysis. The hypothalamus mask results showed that the SON responds to all familiar faces although lateralized on the left for friend and right for sibling, and differential PVN activity related to familiarity between sibling and friend. Taken together, the findings support differential involvement of local hypothalamic substructures, which include the SON and PVN, in response to individuals with varied affiliative significance. Despite the aforementioned limitations, the understanding of the functions of hypothalamic nuclei in affiliative behaviors appears very pertinent in the light of present results and warrants future research efforts. Studies have shown that structural abnormalities of the hypothalamus, specifically in the SON and PVN, are associated with abnormal functions of OXT and AVP in several affective disorders (Schindler et al., 2012) and autism spectrum disorders (Wolfe et al., 2015), all conditions with social dysfunctions. Future research with improved neuroimaging techniques and neuropeptide measurements, enabling more accurate *in vivo* insights on the functions of small hypothalamic nuclei are essential to elucidate the mechanisms underlying social perception and affiliative behaviors critical in social interactions, which may also be beneficial in understanding social dysfunctions in atypical populations (Chaminade, Da Fonseca, Rosset, Cheng, & Deruelle, 2015).

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Disclosure statement

No potential conflict of interest was reported by the authors. AQ8

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